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6-Min Walk Test Provides Prognostic Utility Comparable to Cardiopulmonary Exercise Testing in Ambulatory Outpatients With Systolic Heart Failure

Daniel E. Forman, MD,*† Jerome L. Fleg, MD,‡ Dalane W. Kitzman, MD,§ Clinton A. Brawner, MS,‖ Ann M. Swank, PHD,¶ Robert S. McKelvie, MD, PHD,# Robert M. Clare, MS,** Stephen J. Ellis, PHD,** Mark E. Dunlap, MD,†† Vera Bittner, MD, MSPH‡‡

Boston, Massachusetts; Bethesda, Maryland; Winston-Salem and Durham North Carolina; Detroit, Michigan; Louisville, Kentucky; Hamilton, Ontario, Canada; Cleveland, Ohio; and Birmingham, Alabama

Objectives The goal of this study was to compare the prognostic efficacy of the 6-min walk (6MW) and cardiopulmonary exercise (CPX) tests in stable outpatients with chronic heart failure (HF).

Background CPX and 6MW tests are commonly applied as prognostic gauges for systolic HF patients, but few direct comparisons have been conducted.

Methods Stable New York Heart Association (NYHA) functional class II and III systolic HF patients (ejection fraction ≤35%) from the HF-ACTION (Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training) trial were studied. 6MW distance (6MWD) and CPX indices (peak oxygen consumption [VO_2] and ventilatory equivalents for exhaled carbon dioxide [VE/VCO_2] slope) were compared as predictors of all-cause mortality/hospitalization and all-cause mortality over 2.5 years of mean follow-up.

Results A total of 2,054 HF-ACTION participants underwent both CPX and 6MW tests at baseline (median age 59 years; 71% male; 64% NYHA functional class II and 36% NYHA functional class III/IV). In unadjusted models and in models that included key clinical and demographic covariates, C-indices of 6MWD were 0.58 and 0.65 (unadjusted) and 0.62 and 0.72 (adjusted) in predicting all-cause mortality/hospitalization and all-cause mortality, respectively. C-indices for peak VO_2 were 0.61 and 0.68 (unadjusted) and 0.63 and 0.73 (adjusted). C-indices for VE/VCO_2 slope were 0.56 and 0.65 (unadjusted) and 0.61 and 0.71 (adjusted); combining peak VO_2 and VE/VCO_2 slope did not improve the C-indices. Overlapping 95% confidence intervals and modest integrated discrimination improvement values confirmed similar prognostic discrimination by 6MWD and CPX indices within adjusted models.

Conclusions In systolic HF outpatients, 6MWD and CPX indices demonstrated similar utility as univariate predictors for all-cause hospitalization/mortality and all-cause mortality. However, 6MWD or CPX indices added only modest prognostic discrimination to models that included important demographic and clinical covariates. (J Am Coll Cardiol 2012;60:2653–61) © 2012 by the American College of Cardiology Foundation

Cardiopulmonary exercise (CPX) testing is generally regarded as the gold standard of aerobic assessment (1) with the capacity to reliably discriminate differences along the continuum of low to high exercise performance. This CPX attribute has been incorporated into well-established applications to track performance (e.g., in relation to training or therapy) and as means to distinguish mechanisms underlying dyspnea and/or exercise limitations. CPX is also routinely applied as a prognostic tool. Peak oxygen uptake (VO_2) and the ventilatory equivalents for carbon dioxide (VE/VCO_2) slope are 2 CPX indices that have been extensively validated as function-based prognostic assessments (1–5), both independently and in combination (2,3).

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The distance walked over 6 min is an alternative measure of function that has also been applied as the basis of function-based prognostic assessments (6,7). Compared

From the *Division of Cardiovascular Medicine, Brigham and Women's Hospital, Boston, Massachusetts; †New England Geriatric Research, Education, and Clinical Care, Veterans Administration Boston Healthcare System, Boston, Massachusetts; ‡National Heart, Lung, and Blood Institute, Bethesda, Maryland; §Department of Internal Medicine: Sections on Cardiology and Geriatrics, Wake Forest University Health Sciences, Winston-Salem, North Carolina; ‖Division of Cardiovascular Medicine, Henry Ford Hospital, Detroit, Michigan; ¶Department of Health and Sport Sciences, University of Louisville, Louisville, Kentucky; #Hamilton Health Sciences, Hamilton, Ontario, Canada; **Duke Clinical Research Institute, Durham, North Carolina; ††Heart and Vascular Center, MetroHealth Campus, Case Western Reserve University, Cleveland, Ohio; and the ‡‡Department of Medicine, Division of Cardiovascular Disease, University of Alabama at Birmingham, Birmingham, Alabama. The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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Abbreviations and Acronyms

6MW = 6-minute walk
6MWD = 6-minute walk distance
BMI = body mass index
CI = confidence interval
CPX = cardiopulmonary exercise
ECG = electrocardiogram
HF = heart failure
HR = hazard ratio
IDI = integrated discrimination improvement
LVEF = left ventricular ejection fraction
NYHA = New York Heart Association
VE/VCO_2 = ventilatory equivalents for exhaled carbon dioxide
VO_2 = oxygen consumption

with the nontrivial costs and logistical challenges of CPX testing, a 6-minute walk (6MW) test is significantly less expensive and more convenient. Proponents of the 6MW 4 test also emphasize its distinctive value as a measure of routine activity that may be more clinically relevant than a bicycle- or treadmill-based (7–9) maximal functional evaluation.

We compared the prognostic utility of 6MW and CPX testing using baseline data from the HF-ACTION (Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training) trial (10), a randomized controlled trial of an exercise training intervention for patients with systolic heart failure (HF). The HF-ACTION protocol entailed 6MW and CPX testing on the same day as part of the baseline assessment.

We hypothesized that CPX indices would more accurately discriminate all-cause hospitalization and mortality as well as all-cause mortality over the trial's 2.5-year mean follow-up based on the assumption that gas exchange assessment is more informative than simple distance walked. We also expected that using CPX indices in combination would add to CPX prognostic discrimination.

Methods

Details of the HF-ACTION protocol have been published elsewhere (10). The study enrolled ambulatory systolic HF patients identified by using clinical and echocardiographic criteria (left ventricular ejection fraction [LVEF] ≤35%), who were randomized to treatment with an aerobic exercise training arm with usual care versus usual care alone. 6MW and CPX were completed before randomization. Exercise training entailed 36 supervised outpatient sessions plus home training that was initially combined with the supervised sessions but which then continued independently for the duration of follow-up. The ultimate goal was home training, 5 days a week, using a treadmill or stationary cycle. Patients were followed up over the course of the trial for hospitalizations and mortality. The clinical endpoint committee that monitored these assessments remained blinded to the patients' assignments.

6MW tests were conducted in a standardized format, with explicit instructions provided in the HF-ACTION manual of operations, modeled after prior studies (11–13). Each of the 82 HF-ACTION sites was instructed to measure a 20- to 25-m indoor course and to position a chair at either end, providing subjects a place to rest if necessary. L-shaped hallways were prohibited.

Consistent 6MW test methods were specified in the HF-ACTION manual of operations, including standardized phrasing (e.g., "cover as much ground as possible... keep going... don't worry if you have to sit down or stop to rest...") and consistent timing of encouragement (1-min intervals).

The HF-ACTION protocol was similarly uniform and rigorous with regard to CPX methods. Symptom-limited exercise testing was completed by using commercially available metabolic carts and motor-driven treadmills, employing a modified Naughton protocol (14). The respiratory exchange ratio was used to gauge exercise effort; a ratio >1.1 was targeted as a high effort standard (1).

Peak VO_2 was determined in the CPX Core Laboratory as the highest VO_2 normalized to body mass (VO_2, ml/kg/min) for a given 15- or 20-s interval within the last 90 s of exercise or the first 30 s of recovery, whichever was higher. Mean VE/VCO_2 slope was calculated based on VE/VCO_2 slope data across the entire duration of exercise using the 15- or 20-s averaged data for VCO_2 (l/min) and VE (l/min); this method has previously been demonstrated to maximize VE/VCO_2 prognostic potential (15,16).

Statistical analysis. Statistical analyses were performed by the Data Coordinating Center (Duke Clinical Research Institute, Durham, North Carolina) by using SAS version 9.2 (SAS Institute Inc., Cary, North Carolina). The relationship of 6MW distance (6MWD) to baseline patient characteristics was summarized by using medians with interquartile range of 6MWD across categories of various baseline attributes. Pearson correlation coefficients between baseline characteristics and 6MWD were also calculated for continuous variables.

Unadjusted Pearson correlation coefficients and adjusted partial correlation coefficients were used to assess the association between 6MWD and CPX parameters (peak VO_2 and VE/VCO_2 slope). The same set of covariates was used for both peak VO_2 and VE/VCO_2 to adjust the correlations of the given CPX variable with 6MWD. Covariates used for adjustment comprised all identified predictors from previously developed multivariable linear models of each exercise measurement (6MWD and CPX measures) that were objectively selected by using backward elimination methods (17).

As a measure of the degree to which a model accurately discriminates events from nonevents, C-index estimates with associated 95% confidence intervals (CIs) from unadjusted and adjusted Cox proportional hazards models were used to compare the individual roles of 6MWD and CPX measures (peak VO_2 and VE/VCO_2 slope) with respect to the primary endpoint of all-cause hospitalization or mortality and the secondary endpoint of all-cause mortality. Peak VO_2 and VE/VCO_2 slope were assessed independently and in combination within each prognostic model.

The 95% CI for the C-index in the various models served as a surrogate for hypothesis tests to compare model discrimination. As a general rule, if 2 models of the same

endpoint produce 95% CIs for the C-index that shared no common values, they were regarded as significantly different in terms of discrimination, whereas C-indices with widely overlapping CIs were interpreted as lacking significant differences between the 2 models.

6MWD and CPX indices were assessed within unadjusted models (i.e., 6MWD and CPX indices as univariate predictors) as well as in models adjusted for demographic and clinical covariates. Baseline covariates used for the adjustment were based on Cox proportional hazards models that were previously developed for these endpoints. They were selected using a stepwise method based on a bootstrap-backward selection process (17). Relative risks associated with normalized 6MWD and CPX measures were expressed as hazard ratios (HRs) with 95% CI.

To ensure comparability while optimizing sample size, Cox models were applied to complete case data for patients who had nonmissing values for 6MWD, peak VO_2, and VE/VCO_2 slope. All parameters were converted to standard normal z-scores before their inclusion in the Cox models, and the model assumption of linearity was assessed with respect to each standardized measure. Examination of cubic splines revealed that the relationship of 6MWD to the mortality/hospitalization endpoint was constant beyond 1 SD from the mean value; for this reason, the 6MWD relationship was truncated, and the HR for values of 6MWD >1 SD beyond the mean was set to 1 (i.e., no additional relationship of the measure with death/hospitalization beyond that point).

The integrated discrimination improvement (IDI) statistic was calculated to assess the relative impact of introducing each exercise measure to the models adjusted for demographic and clinical variables (18). The IDI examines models in terms of degree of discrimination, as measured by the separation between mean predicted probabilities among patients with and without endpoints in each model. Continuous variables are expressed as median (25th and 75th percentiles) and discrete variables as percentages. For all analyses, a 2-tailed p value <0.05 was required to reject the null hypothesis.

Table 1 Baseline Characteristics

Parameter	n	Median	IQR: 25th, 75th
Age (yrs)	2,054	59	51, 68
BMI (kg/m^2)	2,049	30.1	26.3, 35.4
Height (cm)	2,049	173	166, 180
6MWD (m)	2,054	372	300, 434
Peak VO_2 (ml/kg/min)	2,030	14.6	11.7, 17.7
VE/VCO_2 slope	2,030	32.4	28.1, 38.3
Sex (male/female)	1,459/595	71%/29%	—
NYHA functional class (class II/class III/IV)	1,317/737	64%/36%	—

6MWD = 6-min walk distance; BMI = body mass index; IQR = interquartile range; NYHA = New York Heart Association; VO_2 = oxygen consumption; VE/VCO_2 = ventilatory equivalents for exhaled carbon dioxide.

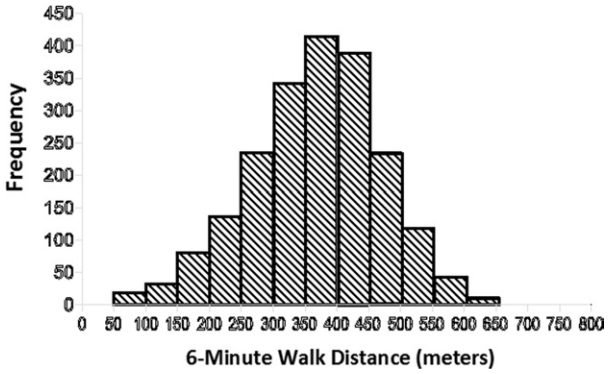

Figure 1 Distribution of 6MWD in the HF-ACTION Study Population

Six-minute walk distance (6MWD) varied widely among participants of the HF-ACTION (Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training) trial, which afforded an excellent opportunity to assess its prognostic efficacy.

Results

Of the 2,331 patients enrolled in HF-ACTION, 211 subjects underwent CPX testing on cycle ergometers and were excluded from the analysis. In 20 other subjects, because it was unclear whether a cycle or treadmill had been used during the CPX test, they also were excluded. Of the 2,100 patients who remained, 2,054 had both 6MW and CPX test data. These 2,054 patients (88% of the original HF-ACTION population) represent the cohort for this analysis. Within this group, 2,030 patients had both 6MWD and peak VO_2 measurements, and 2,013 had 6MWD, peak VO_2, and VE/VCO_2 slope measurements.

Table 1 shows the distribution of baseline patient characteristics in the study population, generally indicative of a middle-aged cohort with mild to moderate functional impairment. Figure 1 illustrates the distribution of 6MWD data, highlighting the wide range of walking capacities and nearly symmetric distribution of 6MWD in the HF-ACTION study population.

Table 2 shows the distribution of 6MWD values according to various key clinical characteristics, with Pearson correlation coefficients for continuous attributes. Older age ($r = -0.23$) and higher body mass index (BMI) ($r = -0.13$) correlated with shorter 6MWD among the continuous variables. Sex, race, New York Heart Association (NYHA) functional class, and other categorical variables also demonstrated significant relationships with 6MWD.

Table 3 shows unadjusted and adjusted correlations between 6MWD and CPX parameters. Significant covariates used in the adjusted model were height, weight, number of hospitalizations during the 6 months before baseline, geographic region, NYHA functional class (II vs. III/IV), age, race, peripheral vascular disease, electrocardiogram (ECG) ventricular conduction abnormality, BMI, sex, LVEF, and diabetes mellitus. Although 6MWD correlated

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Table 2 Distribution of 6MWD According to Baseline Characteristics

Variables	Category	n	6MWD Median (IQR: 25th, 75th)	Pearson Correlation (for Continuous Variables)
Age	<40 yrs	153	407 (346, 457)	−0.23
	40–59	933	385 (307, 450)	
	60–69	558	366 (305, 425)	
	≥70 yrs	410	332 (262, 391)	
BMI	<27.6	676	376 (307, 439)	−0.13
	27.6–33.1	677	383 (307, 442)	
	≥33.1	696	358 (290, 424)	
LVEF	<21.5	676	363 (287, 427)	0.06
	21.5–28.2	673	379 (304, 439)	
	≥28.2	695	373 (310, 434)	
Carvedilol equivalents (mg/day)	Low dose (<30)	1,021	366 (296, 430)	0.04
	High dose (≥30)	1,015	375 (302, 439)	
BDI II	<6	656	387 (322, 442)	−0.12
	6–11	729	373 (301, 439)	
	≥12	664	355 (274, 421)	
Sex	Male	1,459	380 (304, 441)	
	Female	595	354 (290, 415)	
Race	White	1,216	384 (313, 445)	
	Black	697	349 (280, 416)	
	Other	111	385 (320, 439)	
Country	United States	1,874	371 (300, 435)	
	Canada	180	375 (300, 424)	
NYHA functional class	II	1,317	396 (335, 454)	
	III	737	319 (252, 386)	
CCS angina class	No angina	1,695	371 (300, 433)	
	Class I	186	387 (326, 449)	
	Class II–IV	171	356 (282, 410)	
HF etiology	Ischemic	1,043	366 (293, 429)	
	Nonischemic	1,011	380 (307, 442)	
Mitral regurgitation	Low (none to moderate)	1,667	376 (305, 440)	
	High (severe)	227	366 (274, 420)	
ECG vent cond before baseline CPX	Normal	868	378 (305, 442)	
	LBBB	319	385 (315, 449)	
	RBBB	76	366 (305, 427)	
	IVCD	273	366 (296, 420)	
	Paced	469	356 (287, 420)	
Diabetes	No	1,384	384 (314, 442)	
	Yes	670	348 (274, 411)	
PAD	No	1920	374 (304, 436)	
	Yes	124	321 (238, 404)	
COPD	No	1,819	376 (305, 428)	
	Yes	218	327 (262, 405)	

BDI = Beck Depression Index; CCS = Canadian Cardiovascular Society; COPD = chronic obstructive lung disease; CPX = cardiopulmonary exercise; ECG vent cond = electrocardiogram ventricular conduction abnormality; HF = heart failure; IVCD = intraventricular conduction delay; LBBB = left bundle branch block; LVEF = left ventricular ejection fraction; PAD = peripheral arterial disease; RBBB = right bundle branch block; other abbreviations as in Table 1.

significantly with both peak VO_2 and VE/VCO_2 slope, with or without adjustment for covariates, correlations were slightly stronger with peak VO_2 in each case. After adjusting for covariates, correlations of both CPX indices with 6MWD were substantially weaker, indicating the degree to which covariates may have accounted for the unadjusted correlations.

The respective contributions of 6MWD, peak VO_2, and VE/VCO2 slope to unadjusted and adjusted models of all-cause hospitalization/mortality and mortality are shown in Tables 4 and 5, respectively. The HRs were closer to 1 for the given exercise parameter in the adjusted model, compared with the HR in the unadjusted model. However, the C-index was higher in the adjusted model than the unadjusted model; that is, with more variables in the adjusted model, the overall discrimination improved.

Although chi-square tests confirm the significant association of 6MWD, peak VO_2, and VE/VCO_2 slope with both endpoints even after inclusion of common clinical and laboratory covariates, the small IDI estimates associated

Table 3 Correlations of 6MWD to CPX Indices

Parameter	n	Unadjusted Versus Adjusted*	Correlation With 6MWD	p Value
Peak VO_2 (ml/kg/min)	2,030	Unadjusted R	0.54	<0.0001
	1,920	Adjusted R*	0.33	<0.0001
VE/VCO_2 slope	2,014	Unadjusted R	−0.26	<0.0001
	1,905	Adjusted R*	−0.17	<0.0001

*Adjusted correlations are the partial correlations from models including covariates in the final adjusted model of 6MW or any CPX parameter. Abbreviations as in Tables 1 and 2.

with inclusion of these exercise test variables in adjusted models suggest that they contribute only a modest degree of added discrimination. The addition of peak VO_2 to the adjusted model of the primary endpoint (all-cause hospitalization/mortality) produced the highest IDI (0.04), with 6MWD producing an IDI of 0.02 in that model. The IDI was ≤0.01 for the addition of each of these 3 measures to the adjusted model of mortality. The widely overlapping 95% CIs for the C-index estimates of models containing each of the 3 exercise measures, as well as similar IDI values in the adjusted models, suggest that 6MWD and CPX measures do not differ significantly from each another in their prognostic discrimination of these endpoints.

Table 6 displays the C-indices pertaining to normalized 6MWD and CPX measures in models of all-cause hospitalization/mortality and all-cause mortality, respectively. In an unadjusted model of all-cause hospitalization/mortality, the C-index (0.58) associated with 6MWD (truncated at 1 SD above the mean as described earlier) was numerically lower than the C-index of peak VO_2 (0.61) and greater than the C-index associated with VE/VCO_2 (0.56). The 6MWD and CPX measures were also assessed relative to an adjusted model with the covariates: sex, region (United States/non–United States), mitral regurgitation, ECG ventricular conduction abnormality, blood urea nitrogen, LVEF, beta-blocker dose, and the Kansas City Cardiomyopathy Questionnaire, a 23 item disease-specific health status measure for heart failure patients. Without peak VO_2, VE/VCO_2, or 6MWD, the model predicted all-cause hospitalization/mortality, with a C-index of 0.60. Adding 6MWD to the model increased the C-index to 0.62. Adding peak VO_2 (instead of 6MWD) increased the C-index to 0.63. Adding VE/VCO_2 slope (instead of 6MWD or peak VO_2) increased the C-index to 0.61. When peak VO_2 and VE/VCO_2 slope were used in combination within the model, C-index increased to 0.63, no better than the same model minus VE/VCO_2 slope. Combining 6MWD and peak VO_2 within the model increased the C-index to 0.64. However, when all 3 functional indices (6MWD, peak VO_2, and VE/VCO_2 slope) were used in the model together, the C-index remained at 0.64. Notably, when peak VO_2 and VE/VCO_2 slope were entered into the model together, peak VO_2 had a larger influence on prognosis ($p < 0.001$) whereas the impact of the VE/VCO_2 slope was nonsignificant ($p = 0.57$).

Table 6 also displays the C-indices relating 6MWD and CPX measures to all-cause mortality. In unadjusted models, the C-index associated with peak VO_2 (0.68) was slightly higher than the C-index associated with 6MWD (0.65). However, C-indices of 6MWD and VE/VCO_2 slope (0.65) were equivalent. In a model for all-cause mortality with the covariates sex, BMI, loop diuretic dose, Canadian angina class, ECG ventricular conduction abnormalities, LVEF, and serum creatinine, the C-index was 0.69. Adding 6MWD, peak VO2, and VE/VCO2 slope individually to the model increased the C-indices to 0.72, 0.73, and 0.71, respectively. Combining the functional indices modestly increased prognostic discrimination; the C-index increased to 0.74 with any combination of the functional indices (C-index = 0.74 in relation to 6MWD and peak VO_2 or to peak VO_2 and VE/VCO_2 slope or to 6MWD, peak VO_2, and VE/VCO_2 slope).

Table 4 Prognostic Utility of 6MWD Versus CPX Indices in Predicting All-Cause Hospitalization/Mortality

Model	Parameter	Chi-Square Statistic	p Value	Hazard Ratio* (95% Confidence Interval)	C-Index (95% Confidence Interval)	IDI†
Unadjusted univariate predictors	6MWD‡ (Z <1)	99	<0.0001	0.75 (0.70–0.79)	0.58 (0.57–0.60)	
	Peak VO_2	158	<0.0001	0.69 (0.65–0.73)	0.61 (0.59–0.62)	
	VE/VCO_2 slope	85	<0.0001	1.27 (1.21–1.33)	0.56 (0.55–0.58)	
Adjusted§	6MWD‡ (Z <1)	48	<0.0001	0.78 (0.73–0.84)	0.62 (0.60–0.64)	0.019
	Peak VO_2	80	<0.0001	0.72 (0.67–0.77)	0.63 (0.61–0.65)	0.043
	VE/VCO_2 slope	19	<0.0001	1.15 (1.08–1.22)	0.61 (0.59–0.62)	0.009

*Hazard ratio based on *z*-score. †Integrated discrimination improvement (IDI) model includes 2,013 patients with nonmissing values for 6MW, peak VO_2, and VE/VCO_2. ‡6MWD (normalized) is truncated at 1 SD in the model of hospitalization/mortality because of its lack of relationship with this endpoint beyond that point. Truncation in this case implies that the hazard ratio for values of 6MWD >1 is set to 1. Other truncated covariates are carvedilol equivalent dose: truncated above 50 mg/day; BMI: truncated above 25 kg/m^2; creatinine: truncated above 2.3 mg/dl. §All-cause hospitalization/mortality model adjusted for sex, region (United States vs. non–United States), mitral regurgitation, ECG vent cond, blood urea nitrogen, LVEF, carvedilol equivalent dose, and Kansas City Cardiomyopathy Questionnaire symptom stability score. All-cause mortality model adjusted for sex, BMI, loop diuretic dose, angina class, ECG vent cond, LVEF, and creatinine.
Other abbreviations as in Tables 1 and 2.

Table 5 Prognostic Utility of 6MWD Versus CPX Indices in Predicting All-Cause Mortality

Model	Parameter	Chi-Square Statistic	p Value	Hazard Ratio* (95% Confidence Interval)	C-Index (95% Confidence Interval)	IDI
Unadjusted univariate predictors	6MWD	94	<0.0001	0.61 (0.55–0.67)	0.65 (0.62–0.68)	
	Peak VO_2	123	<0.0001	0.48 (0.42–0.55)	0.68 (0.65–0.71)	
	VE/VCO_2 slope	130	<0.0001	1.58 (1.46–1.71)	0.65 (0.61–0.68)	
Adjusted†	6MWD	55	<0.0001	0.65 (0.57–0.73)	0.72 (0.69–0.75)	0.005
	Peak VO_2	77	<0.0001	0.51 (0.44–0.59)	0.73 (0.71–0.76)	0.010
	VE/VCO_2 slope	45	<0.0001	1.37 (1.25–1.51)	0.71 (0.68–0.74)	0.004

*Hazard ratio based on *z*-score. †All-cause hospitalization/mortality model adjusted for sex, region (United States vs. non–United States), mitral regurgitation, ECG vent cond, blood urea nitrogen, LVEF, carvedilol equivalent dose, and Kansas City Cardiomyopathy Questionnaire symptom stability score. All-cause mortality model adjusted for sex, BMI, loop diuretic dose, angina class, ECG vent cond, LVEF, and creatinine.

Other abbreviations as in Tables 1 and 2.

Discussion

In this secondary analysis from HF-ACTION, we found that a 6MW test provides useful prognostic information for both the composite outcome of all-cause hospitalization/mortality as well as the outcome of all-cause mortality in NYHA functional class II and III HF outpatients receiving state-of-the-art therapy for systolic HF. In both unadjusted and adjusted models, the prognostic information provided by 6MWD, as estimated by using the C-index, was similar to that for peak VO_2 and VE/VCO_2 slope attained by using CPX testing even when peak VO_2 and VE/VCO_2 slope were assessed in combination. Although the C-statistic to predict all-cause hospitalization/mortality and all-cause mortality for CPX testing was numerically larger than that for 6MWD, the difference was too small to be clinically meaningful. Individually, 6MWD and peak VO_2 provided similar levels of discrimination as univariate predictors; unadjusted models of either exercise parameter predicting hospitalization/mortality or all-cause mortality had discrimination that approached that of models with known clinical and demographic covariates without exercise parameters. However, there was little augmentation in discrimination resulting from the addition of either exercise measure to the adjusted models.

Table 7 lists many of the landmark studies (2,19–27) that validated the 6MW test as a prognostic measure for systolic HF patients and those which compared it with CPX testing. These and related studies (28–31) were small; enrolled patients with different etiologies and severities of HF; and used variable protocols to administer the tests. Heterogeneity of results is thus not surprising (31).

Compared with previous studies, HF-ACTION stands out for its larger study population, comprehensive assessments, and emphasis on contemporary evidence–based therapy. Our data are noteworthy in showing efficacy of 6MWD as a continuous prognostic marker among a large HF population with a wide range of performance capacities, nearly all of whom were receiving beta-blockers, angiotensin-converting enzyme inhibitors, or angiotensin receptor blockers. Whereas prior literature demonstrated greatest 6MWD prognostic discrimination for patients with very low performance, in the current study, 6MWD was predictive across a wide spectrum of performance capacities and essentially matched the efficacy of CPX testing as a prognostic tool across the full range of patients.

A notable attribute of the HF-ACTION protocol was that it provided explicit instructions on how to implement

Table 6 C-Index of 6MWD Versus CPX Indices in Unadjusted and Adjusted Models of All-Cause Hospitalization/Mortality and All-Cause Mortality

	All-Cause Hospitalization/Mortality		All-Cause Mortality	
Variable	Unadjusted	Adjusted	Unadjusted	Adjusted
Model without 6MWD, peak VO_2, or VE/VCO_2 slope	NA	0.60	NA	0.69
Model with 6MWD*	0.58	0.62	0.65	0.72
Model with peak VO_2	0.61	0.63	0.68	0.73
Model with VE/VCO_2 slope	0.56	0.61	0.65	0.71
Model with peak VO_2 and VE/VCO_2 slope	0.61	0.63	0.70	0.74
Model with peak VO_2 and 6MWD*	0.61	0.64	0.69	0.74
Model with peak VO_2 and VE/VCO_2 slope and 6MWD*	0.61	0.64	0.71	0.74
	Model parameters are sex, region, mitral regurgitation, ECG vent cond, BUN, LVEF, carvedilol equivalent dose, KCCQ symptom stability score		Model parameters are sex, BMI, loop diuretic dose, angina class, ECG conduct abnl, LVEF, Cr	

Unadjusted model contains only the stated exercise variable(s). Adjusted model includes the given exercise variable(s) plus the model covariates listed. *6MWD (normalized) is truncated at 1 SD in the model of hospitalization/mortality because of its lack of relationship with this endpoint beyond that point. Truncation in this case implies that the hazard ratio for values of 6MWD >1 is set to 1. Other truncated covariates are carvedilol equivalent dose: truncated above 50 mg/day; BMI: truncated above 25 kg/m^2; and creatinine (Cr): truncated above 2.3 mg/dl.

BUN = blood urea nitrogen; KCCQ = Kansas City Cardiomyopathy Questionnaire; NA = not applicable; region = United States versus non–United States; other abbreviations as in Tables 1 and 2.

Table 7 6MW Test to Predict HF Outcomes and Studies Comparing 6MW and CPX

Prior Study	Study Population	Results
6MW test as a prognostic marker		
Bittner et al. (19)	833 patients • LVEF 37 ± 14% • NYHA functional class 1.8 • 15% on beta-blockers	<300 m quartile: Significantly greater chance of death (10.23% vs. 2.99%; p = 0.01), hospitalization (40.91% vs. 19.90%; p = 0.002), and HF hospitalization (22.16% vs. 1.99%; p < 0.0001).
Bettencourt et al. (20)	139 patients • LVEF 33.5 ± 13.2% • NYHA functional class 1.9; • 25.2% on beta-blockers	<350 m independently predicted all-cause mortality
Ingle et al. (21)	1,592 HF patients • Mean LVEF 48%; range 35%–56% • NYHA functional class I–IV (specific proportions not clarified) • 42.2% on beta-blockers	6MWD independently predicted mortality among patients with >mild left ventricular systolic dysfunction
6MW test for prognostication compared with CPX test		
Cahalin et al. (22)	45 patients • LVEF 20 ± 6% • NYHA functional class 3.3 • Beta-blocker unreported	• 6MWD correlated with peak VO_2 (r = 0.64, p < 0.001) • 6MWD <300 m predicted a combined endpoint of death and/or hospitalization for transplant (p = 0.04)
Roul et al. (23)	121 patients • LVEF 29 ± 13 • NYHA functional class 2.4 • Beta-blocker unreported	• 6MWD correlated to peak VO_2 for patients who walked ≤300 m (r = 0.65) • Events significantly higher in those who walked ≤300 m
Zugck et al. (24)	113 patients • LVEF 19 ± 7% • NYHA functional class 2.2 • 17% using beta-blocker	• 6MWD correlated strongly with peak VO_2 (r = 0.68) • 6MWD prognostic assessment similar to peak VO_2
Lucas et al. (25)	307 patients • LVEF 23% average • Patients under evaluation for transplant	• Shorter 6MWD correlated to lower peak VO_2 • Peak VO_2 predicted survival, but 6MWD did not
Opasich et al. (26)	315 HF patients • Mean LVEF 26 ± 8% • NYHA functional class 2.4 • Beta-blocker not reported	• 6MWD is a univariate prognostic marker • When entered into a model with NYHA and peak VO_2, prognostic value of 6MWD diminished
Guazzi et al. (2)	253 HF patients • LVEF 36.3 ± 11.4% • NYHA functional class 2.2 ± 0.78 • 58.5% on beta-blockers	• 6MWD correlated with peak VO_2 and VE/VCO_2 slope but did not predict mortality
Rostagno et al. (27)	214 patients • LVEF 42% • NYHA functional class 2.1 • 25% on beta-blockers	• Survival significantly lower among those who walked <300 m • Peak VO_2 provided no prognostic value

Abbreviations as in Tables 1 and 2.

the 6MW test. Although proponents of the 6MW test often emphasize the ease and convenience of its application, inconsistencies in its administration may inadvertently diminish the reliability of the results (32). In HF-ACTION, significant efforts were undertaken to standardize optimal techniques for both 6MW and CPX testing, thus providing a robust comparison between these 2 performance assessments.

Baseline 6MWD correlated more strongly with peak VO_2 than with VE/VCO_2 slope, suggesting that 6MWD and peak VO_2 share more physiological underpinnings (33). Cardiac output, peripheral perfusion capacity, and skeletal muscle health are integral to each of these performance measures, and differ from the physiological determinants underlying VE/VCO_2 slope (e.g., ventilation-perfusion abnormalities, chemoreceptor responses, intrinsic respiratory capacity, cardiopulmonary coupling) (3). Although we therefore expected that VE/VCO_2 slope would add independent value to the prognostic model that included peak VO_2, this was not the case. VE/VCO_2 slope added only minor prognostic enhancement.

The prognostic efficacy of 6MWD demonstrated in this analysis resonates with a multitude of recent literature highlighting the prognostic utility of other walking assessments such as gait speed and the 400-m corridor walk (34,35). The physiological principles underlying these different assessments of walking capacity seem similar, and reinforce the value of the 6MW test as a valid, sensitive, and clinically meaningful prognostic tool.

Strengths and limitations. As the largest randomized controlled trial of exercise training ever conducted in HF patients, HF-ACTION provided an unparalleled opportunity to compare the prognostic utility of 6MW and CPX testing in

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this common clinical setting. Thus, the large sample size and rigorous protocol for performing both tests in a contemporary HF population receiving evidence-based drug and device therapy represent major strengths of the current study.

Certain limitations should also be recognized. Because HF-ACTION is an exercise training trial, the exercise intervention may have affected the relationship between functional assessments and outcomes. However, this treatment effect has similar bearing on 6MW and CPX assessments and does not confound the analysis.

Although CPX tests were repeated on approximately 400 HF-ACTION subjects to exclude familiarization (36), similar assessments of possible familiarization effects were never made in relation to 6MW tests in HF-ACTION. Other studies have suggested this may have bearing on 6MWD assessments (37). Therefore, it cannot be assumed that 6MWD assessments will consistently provide equivalent prognostic discrimination when used for serial evaluations. Nonetheless, the fact that the initial 6MWD assessments yielded prognostic information similar to that of CPX tests suggests that the predictive implications of walking distance are robust.

Although HRs associated with standardized values of 6MWD and the CPX measures are provided in the tables, comparisons of these ratios should be made with caution. Given the fundamental differences in the nature of the various exercise measures, the risk associated with 1 SD difference in a given measure may not be directly comparable to the risk associated with an equivalent difference in another measure. The HF-ACTION protocol entailed completing 6MW and CPX testing at the same baseline visit, eliminating fluctuations in mood, health, or other clinical dynamics that would have been more likely if tests were performed on separate days. However, the protocol did not randomize the order in which the 6MW and CPX tests were conducted; because the 6MW test generally preceded the CPX test, this may have biased the results.

Although our data indicate that 6MWD or CPX indices peak VO_2 and VE/VCO_2 slope add only modest prognostic value to models that already include demographic and clinical covariates that could be gathered as part of a comprehensive clinical assessment, both tests provide useful assessments of a patient's aerobic capacity. In addition, CPX testing may be more likely to detect exercise-related hemodynamic instability, ischemia, arrhythmias, and symptoms that are clinically important (1) but that were outside the focus of this investigation.

Finally, in addition to peak VO_2 and VE/VCO_2 slope, CPX provides the potential to assess several additional indices that may increase prognostic information. Oscillatory expiratory breathing, end-tidal partial pressure of carbon dioxide, VE/VO_2 ratios, recovery gas exchange dynamics, and heart rate and blood pressure responses are among an extensive array of CPX assessments that can be used to enhance prognostic assessment (1,2,38). Although this study highlights the utility of 6MWD relative to the 2 most commonly reported indices of CPX testing, it does not address the utility of a comprehensive CPX evaluation.

Conclusions

The 6MW test provided useful prognostic information for all-cause hospitalization and mortality among stable NYHA functional class II and III HF patients receiving state-of-the-art therapy. Although CPX testing is often assumed to provide superior function-based prognostic assessment in HF patients, we demonstrated that 6MWD provided prognostic value that was similar to peak VO_2, VE/VCO_2 slope, and their combination in a relatively stable HF population. These data suggest that a 6MW test may be substituted for CPX testing as an inexpensive, practical clinical tool to help gauge prognosis in the large and growing HF population. Although 6MWD and peak VO_2 both demonstrated utility as univariate predictors in unadjusted prognostic models for all-cause hospitalization/mortality and all-cause mortality, both measures added only modest prognostic discrimination to models that included important demographic and clinical covariates.

Reprint requests and correspondence: Dr. Daniel E. Forman, Division of Cardiovascular Medicine, Brigham and Women's Hospital, 75 Francis Street, Boston, Massachusetts 02115. E-mail: deforman@partners.org.

REFERENCES

1. Balady GJ, Arena R, Sietsema K, et al. Clinician's guide to cardiopulmonary exercise testing in adults: a scientific statement from the American Heart Association. Circulation 2010;122:191–225.
2. Guazzi M, Dickstein K, Vicenzi M, Arena R. Six-minute walk test and cardiopulmonary exercise testing in patients with chronic heart failure: a comparative analysis on clinical and prognostic insights. Circ Heart Fail 2009;2:549–55.
3. Arena R, Myers J, Guazzi M. The clinical and research applications of aerobic capacity and ventilatory efficiency in heart failure: an evidence-based review. Heart Fail Rev 2008;13:245–69.
4. Arena R, Myers J, Guazzi M. Cardiopulmonary exercise testing is a core assessment for patients with heart failure. Congest Heart Fail 2011;17:115–9.
5. Forman DE, Myers J, Lavie CJ, et al. Cardiopulmonary exercise testing: relevant but underused. Postgrad Med 2010;122:68–86.
6. Faggiano P, D'Aloia A, Gualeni A, et al. The 6 minute walking test in chronic heart failure: indications, interpretation and limitations from a review of the literature. Eur J Heart Fail 2004;6:687–91.
7. ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med 2002;166:111–7.
8. Du H, Newton PJ, Salamonson Y, et al. A review of the six-minute walk test: its implication as a self-administered assessment tool. Eur J Cardiovasc Nurs 2009;8:2–8.
9. Solway S, Brooks D, Lacasse Y, Thomas S. A qualitative systematic overview of the measurement properties of functional walk tests used in the cardiorespiratory domain. Chest 2001;119:256–270.
10. O'Connor CM, Whellan DJ, Lee KL, et al. Efficacy and safety of exercise training in patients with chronic heart failure: HF-ACTION randomized controlled trial. JAMA 2009;301:1439–50.
11. Kavanaugh T, Meyers MG, Baigrie RS, et al. Quality of life and cardiorespiratory function in chronic heart failure: effects of 12 months' aerobic training. Heart 1996;76:42–9.

12. Meyer K, Schwaibold M, Westbrook S, et al. Effects of exercise training and activity restriction on 6-minute walking test performance in patients with chronic heart failure. Am Heart J 1997;133:447–53.
13. Guyatt GH, Sullivan MJ, Thompson PJ, et al. The 6-minute walk: a new measure of exercise capacity in patients with chronic heart failure. Can Med Assoc J 1985;132:919–23.
14. Patterson JA, Naughton J, Pietras RJ, Gunnar RM. Treadmill exercise in assessment of patients with cardiac disease. Am J Cardiol 1972;30: 757–62.
15. Arena R, Myers J, Abella J, et al. Development of a ventilatory classification system in patients with heart failure. Circulation 2007; 115:2410–7.
16. Arena R, Humphrey R, Peberdy MA. Prognostic ability of VE/VCO_2 slope calculations using different exercise test time intervals in subjects with heart failure. Eur J Cardiovasc Prev Rehabil 2003;10:463–8.
17. O'Connor CM, Whellan DJ, Wojdyla D, et al. Factors related to morbidity and mortality in patients with chronic heart failure with systolic dysfunction: the HF-ACTION predictive risk score model. Circ Heart Fail 2012;5:63–71.
18. Pencina MJ, D'Agostino RB Sr., D'Agostino RB Jr., Vasan RS. Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. Stat Med 2008;27:157–72.
19. Bittner, V, Weiner DH, Yusuf S, et al. Prediction of mortality and morbidity with a 6-minute walk test in patients with left ventricular dysfunction. SOLVD Investigators. JAMA 1993;270:1702–7.
20. Bettencourt P, Ferreira A, Dias P, et al. Predictors of prognosis in patients with stable mild to moderate heart failure. J Card Fail 2000;6:306–13.
21. Ingle L, Rigby AS, Carroll S, et al. Prognostic value of the 6 min walk test and self-perceived symptom severity in older patients with chronic heart failure. Eur Heart J 2007;28:560–8.
22. Cahalin, LP, Mathier MA, Semigran MJ, Dec GW, DiSalvo TG. The six-minute walk test predicts peak oxygen uptake and survival in patients with advanced heart failure. Chest 1996;110:325–32.
23. Roul G, Germain P, Bareiss P. Does the 6-minute walk test predict the prognosis in patients with NYHA class II or III chronic heart failure? Am Heart J 1998;136:449–57.
24. Zugck C, Krüger C, Dürr S, et al. Is the 6-minute walk test a reliable substitute for peak oxygen uptake in patients with dilated cardiomyopathy? Eur Heart J 2000;21:540–9.
25. Lucas C, Stevenson LW, Johnson W, et al. The 6-min walk and peak oxygen consumption in advanced heart failure: aerobic capacity and survival. Am Heart J 1999;138:618–24.
26. Opasich C, Pinna GD, Mazza A, et al. Six-minute walking performance in patients with moderate to severe heart failure. Eur Heart J 2001;22:488–96.
27. Rostagno C, Olivo G, Comeglio M, et al. Prognostic value of 6-minute walk corridor test in patients with mild to moderate heart failure: comparison with other methods of functional evaluation. Eur J Heart Fail 2003;5:247–52.
28. Rubim VA, Neto CD, Romeo JL, Montera MW. Prognostic value of the six-minute walk test in heart failure. Arq Bras Cardiol 2006;86: 120–5.
29. Arslan S, Erol MKE, Gundogdu F, et al. Prognostic value of the six-minute walk test in stable outpatients with heart failure. Tex Heart Inst J 2007;34:166–9.
30. Olsson LG, Swedberg K, Clark AL, et al. Six minute corridor walk test as an outcome measure for the assessment of treatment in randomized, blinded intervention trials of chronic heart failure: a systematic review. Eur Heart J 2005;26:778–93.
31. Casanova C, Celli BR, Barria P, et al. The 6-min walk distance in healthy subjects: reference standards from seven countries. Eur Respir J 2011;37:150–6.
32. Guyatt GH, Pugsley SO, Sullivan MJ, et al. Effect of encouragement on walking test performance. Thorax 1984;39:818–22.
33. Carvalho EE, Costa DC, Crescêncio JC, et al. Heart failure: comparison between six-minute walk test and cardiopulmonary test. Arq Bras Cardiol 2011;97:59–64.
34. Studenski S, Perera S, Patel K, et al. Gait speed and survival in older adults. JAMA 2011;305:50–8.
35. Newman AB, Simonsick EM, Naydeck BL, et al. Association of long-distance corridor walk performance with mortality, cardiovascular disease, mobility limitation, and disability. JAMA 2006;295:2018–26.
36. Bensimhon DR, Leifer ES, Ellis SJ, et al. Reproducibility of peak oxygen uptake and other cardiopulmonary exercise testing parameters in patients with heart failure (from the Heart Failure and A Controlled Trial Investigating Outcomes of exercise traiNing). Am J Cardiol 2008;102:712–7.
37. Wu G, Sanderson B, Bittner V. The 6-minute walk test: how important is the learning effect? Am Heart J 2003;146:129–33.
38. Sun XG, Hansen JE, Beshai JF, Wasserman K. Oscillatory breathing and exercise gas exchange abnormalities prognosticate early mortality and morbidity in heart failure. J Am Coll Cardiol 2010;55:1814–23.

Key Words: cardiopulmonary exercise testing ■ heart failure ■ prognosis ■ walking test.